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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,821	10/16/2003	Eric Wickstrom	W1133/20008	2530

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
03/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-75,80,82,83 and 86-101* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,17-25,35-40,46,47,53,57-68,74 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80-83,86 and 88-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 76-79, 81, 84, and 85 have been cancelled. Claims 5, 6, 15, 17-25, 35-40, 46, 47, 53, 57-68, 74, and 87 have been withdrawn. Claims 93-101 are new. Claim 88 has been amended.

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80-83, 86, and 88-101 are under examination.

2. All rejections/objections pertaining to claim 85 are moot because Applicant cancelled the claim in the response filed on 12/19/2007.

Response to Arguments

Claim Rejections - 35 USC § 103

3. Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-92 remain and the new claims 93-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166), in view of both Meade et al. (US Patent No. 6,713,046) and Basu et al. (Bioconjugate Chem, 1997, 8: 481-488) for the reasons of record set forth in the non-final Office action of 07/26/2007. Applicant's arguments filed 12/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Tomalia et al. actually teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52 (column 18, lines 23-67, column 19, lines 1-67, column 20, lines 1- 29, column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds. However, Applicant argues, the instant application discloses a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not taught by Tomalia et al., to the problem of steric hindrance between the three functional units of the claimed compound. With respect to the Examiner's assertion that Tomalia et al. teach two or more dendrimers associated with each other (covalently bridged or through other associations, citing claim 12 of the '166 patent), Applicant argues that Tomalia et al. discloses that (column 17, lines 41-67):

"As used herein, "associated with" means that the carried material(s) can be physically encapsulated or entrapped within the core of the dendrimer, dispersed partially or fully throughout the dendrimer, or attached or linked to the dendrimer or any combination thereof, whereby the attachment or linkage is by means of covalent bonding, hydrogen

bonding, adsorption, absorption, metallic bonding, van der Waals forces or ionic bonding, or any combination thereof."

Applicant argues that, while this section of the Tomalia specification comprises a general statement listing all envisioned kinds of bonding, Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" (column 47, lines 55-62). Applicant argues that the other recitations of the (T)e*(P)x*(M)y structure (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA and that at no point Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples. Therefore, Applicant argues, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers. In addition, Applicant submits that the order of functional units in the claimed compound X-L1-P-L2-T is vital to the purpose of entering a cell, then binding to a nucleic acid target; the compound (T)e*(P)x*(M)y taught by Tomalia et al. permits compound binding to multiple neighboring cells via multiple T interactions on the surface of the dendrimer P, preventing internalization of the compound into a single targeted cell, which in turn will prevent PNA binding to the targeted nucleic acid inside the cell. With respect to the Examiner's assertion that the arrangement is not significant if it does not provide a novel feature, Applicant submits that he has attempted to utilize the PAMAM dendrimer designed by Tomalia, despite the teaching of the Tomalia patent that genetic material was never covalently bonded to PAMAM, as set forth on the Declaration under 37 CFR 1.132 of Dr. Eric Wickstrom, filed herewith; as set forth on

the Declaration (paragraphs 8-12), the attempt to produce this construct failed. Applicant submits that the federal Circuit has held that if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) MPEP 2143.01; the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu to teach or suggest the claimed invention, however, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant argues, he had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Therefore, Applicant argues, attempting to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Applicant submits that there is no suggestion in the Tomalia et al. to modify their teaching to yield the present invention; Tomalia et al. would not have motivated one of skill in the art to reach the claimed invention when it teaches that genetic material can be complexed with a dendrimer only via a non-covalent association (column 47, lines 55-62). Applicant argues that, following Tomalia et al., one of skill in the art would have lacked the motivation to use

their teachings alone or in combination with the teachings of the secondary references to make the composition of the present invention with a reasonable expectation of success; absent such reasonable motivation, there can be no *prima facie* case of obviousness. Applicant argues that the secondary references Meade and Basu do not remedy the aforementioned deficiency of Tomalia et al. For these reasons Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer carrying the therapeutic moiety M (i.e., P-M is equivalent to the claimed diagnostic or therapeutic moiety X) and wherein T represents a targeting moiety such as a single-stranded nucleic acid and wherein T is attached to the dendrimer via a linker (i.e., covalent attachment), wherein the linker is used to avoid steric hindrance (column 17, lines 40-60 column 22, lines 15-35, column 28, lines 10-27); because Tomalia et al. teach avoiding steric hindrance by using linkers, Applicant's argument that the linkers are a non-obvious solution to the problem of steric hindrance is not found persuasive. Therefore, Tomalia et al. teach a compound with the formula X-L1-T, wherein T can be a single-stranded nucleic acid. Tomalia et al. teach that the targeting moiety can be used to deliver the therapeutic moiety to a gene within the cell, i.e., antisense DNA (column 23, lines 1-10). Therefore, Tomalia et al. do teach covalently binding nucleic acids to their dendrimers, wherein the nucleic acids can be used to deliver the therapeutic/diagnostic moiety to a specific target inside the cell.

While Tomalia et al. teach a compound having the formula X-L1-T, wherein T is an antisense DNA, they do not specifically teach PNA. However, Basu et al. teach the advantages of using PNAs as compared to antisense DNA; they also teach conjugating the PNA with a peptide analog of insulin-like growth factor 1 for increased cellular uptake of the PNA, wherein the PNA and the peptide analog are covalently linked by a (Gly)4 linker (Abstract, p. 481, column 2, p. 482, column 1, Fig. 2). Therefore, one of skill in the art would have known to replace the antisense DNA of Tomalia et al. with a PNA-peptide of Basu et al. By doing such, one of skill in the art would have obtained a compound having the formula X-L1-P-L2-T. Therefore, Applicant's argument that the compound of Tomalia et al. permits binding to multiple neighboring cells via multiple T interactions on the surface of the dendrimer, preventing internalization of the compound into a single target cell thus preventing the binding of PNA to the nucleic acid inside the cell is not found persuasive; the combined teachings of Tomalia et al. and Basu et al. disclose a compound identical to the claimed compound, and therefore, they must necessarily have identical properties. For the same reasons, the argument that the combination of Tomalia et al. and Meade et al. requires the eradication of the intended function of the references is not supported by evidence; it is the combination of Tomalia et al., Basu et al., and Meade et al. which teaches the claimed invention, as noted above. The argument that Tomalia et al. teach that the genetic material to be delivered is not associated with the dendrimer by a covalent bond is irrelevant, because it refers to the therapeutic moiety X (defined by the claims as the material to be delivered

attached to the dendrimers) and the claims do not require a covalent bond to form X (i.e., attaching the therapeutic material to the dendrimer via a covalent bond).

The declaration under 37 CFR 1.132 filed on 12/19/2007 is insufficient to overcome the instant rejection. Tomalia et al. clearly teach that single-stranded DNA can be attached to their dendrimers via linkers. It is noted that the instant specification teaches that dendrimers can be prepared such that they have reactive groups capable of being attached to a variety of compounds including PNA and linkers and that techniques of attaching PNA to the dendrimers are within the skill in the art (p. 11, lines 6-20, p. 17, lines 17 and 18); therefore, the declaration is not consistent with the teachings in the specification. Additionally, the prior art teaches the successful solid phase synthesis of targeting ligand-PNA conjugates (see Basu et al.). One of skill in the art would know how to couple a dendrimer to the solid phase-attached and protected ligand-PNA; the declaration does not provide any evidence that this is not possible and moreover, the specification teaches that one of skill in the art would easily link a dendrimer to a ligand-PNA. The fact that Applicant used a slightly different method, i.e., extending the dendrimer from the solid phase attached ligand-PNA as opposed to attaching the dendrimer to the solid phase-attached ligand-PNA, does not render the invention patentable. It is noted that the claimed invention is drawn to a composition and the method of obtaining the composition is irrelevant for patentability if it results in the same product, which is the instant case. Therefore, Applicant's argument of the requirement of a substantial reconstruction and redesign of the elements shown in the

primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate is not found persuasive.

With respect to the limitations recited in claims 93-95, it would have been obvious to one of skill in the art to optimize the linker length for better results. With respect to the limitations recited in claims 96-98, absent evidence of unexpected results, it would have been obvious to the ordinary skilled artisan to use routine experimentation to try different linkers with the purpose of optimizing the results; it is noted that one of skill in the art would have known to use hydrophilic linkers because such linkers are well described in the prior art. With respect to the limitations recited in claims 99-100, it is noted that the dendrimers of Tomalia et al. are branched (column 2, lines 32-65).

4. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, 88-92 remain and the new claims 93-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. (Molecular Therapy, 2001, 3: 491-499) for the reasons of record set forth in the non-final Office action of 07/26/2007. Applicant's arguments filed 12/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Nakano et al. do not cure the deficiencies of Tomalia et al., Meade et al., and Basu et al. The rejection is maintained because Tomalia et al., Meade et al., and Basu et al. do teach the claimed invention for the reasons set forth above.

5. Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, 89-92 remain and the new claims 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), in view of both Liang et al. (Molecular Therapy, 2000, 3: 236-243, of record) and Basu et al. for the reasons of record set forth in the non-final Office action of 07/26/2007. Applicant's arguments filed 12/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Lewis et al. teach a DOTA-PNA conjugate designed to target bcl-2 (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., the targeting moiety does not bind to a cell surface molecule as required by the instant claims). Additionally, Applicant argues, the Lewis reference teaches direct bonding of the non-specific peptide and a radionuclide-containing moiety to the PNA, which is in contrast to the instantly claimed compounds, in which linking moieties are used to connect the targeting sequence and treatment moieties to the PNA. With respect to Liang et al., Applicant argues that they teach transferrin-PNA conjugates wherein no cellular uptake is observed unless the transferrin-PNA is mixed with a plasmid vector associated with PEI. Therefore, Applicant argues, Liang et al. provide no motivation to design the present compounds without the concurrent use of PEI. Additionally, Applicant argues, the compound of Liang et al. lacks the specificity provided by the present invention because transferrin

receptor is ubiquitously expressed. Therefore, Applicant argues, the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of Lewis et al. and Liang et al. which teaches a targeting ligand capable of binding to a cell surface molecule. The argument that the ligand of Liang et al. lacks the specificity provided by the present invention is not found persuasive because specificity is not claimed; the claims only targeting moiety capable of binding a cell surface molecule, which the transferrin of Liang et al. does. Even if the claims would recite specific delivery, it is noted that Basu et al. teach specific targeting moieties (see above), and therefore, one of skill in the art would have known to use their targeting moiety to achieve delivery to specific cells. Applicant argues that the transferrin-PNA of Liang et al. is not taken up by cells in the absence of PEI, and therefore, Liang et al. provide no motivation to design the present compounds without the concurrent use of PEI. This argument is not found persuasive because one of skill in the art would know that the DOTA of Lewis et al. could substitute for PEI, since both are known in the art to be efficient at delivery of nucleic acids to the cells. With respect to the lack of linkers in the compound of Lewis et al., it is noted that Basu et al. teach

the inclusion of linkers between PNA and the targeting moiety, wherein the linkers are used to avoid steric hindrance (p. 482, column 2, Fig. 2). Therefore, one of skill in the art would have known and would have been motivated to use linkers to attach the targeting and therapeutic moieties to PNA; one of skill in the art would have known that, by doing so, functional interference between the PNA and the moieties attached to it would be avoided. For these reasons, the references provided by the Applicant demonstrating PEI toxicity and the necessity of specific delivery (i.e., Sun et al., Bioconjug Chem, 2005, 16: 294-305; Ochietti et al., Gene Ther, 2002, 9: 939-945; Kratz et al., J Drug Targeting, 2000, 8: 305-318) are not sufficient to overcome the instant rejection.

With respect to the limitations recited in claims 93-95, it would have been obvious to one of skill in the art to optimize the linker length for better results.

6. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-92 remain and the new claims 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al. for the reasons of record set forth in the non-final Office action of 07/26/2007. Applicant's arguments filed 12/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Nakano et al. do not cure the deficiencies of over Lewis et al. taken with Liang et al. and Basu et al. The

rejection is maintained because over Lewis et al. taken with Liang et al. and Basu et al. do teach the claimed invention for the reasons set forth above.

7. Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, 88-92 remain and the new claims 93-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al. for the reasons of record set forth in the non-final Office action of 07/26/2007. Applicant's arguments filed 12/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Lewis et al. taken with Liang et al. and Basu et al. do not teach the claimed invention and this deficiency is not cured by Tomalia et al. or Meade et al. as set forth above and as evidenced by the 1332 declaration.

Applicant's arguments are acknowledged, however, they are not found persuasive for the reasons set forth above. Additionally, the 132 declaration is not sufficient to overcome the instant rejection for the reasons set forth above.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

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